DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19-815
ANDAs 77-746, 76-449, 76-577, 76-514, 76-725

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

August 16, 2010

Shire Development, Inc.
Attn: Linda Mota
725 Chesterbrook Blvd.
Wayne, PA 19087

Mylan Pharmaceuticals, Inc.
Attn: Wayne Talton
781 Chestnut Ridge Road
Morgantown, WV 26505

Impax Laboratories, Inc.
Attn: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Upsher-Smith Laboratories, Inc.
Attn: Mark B. Halvorsen, Pharm.D.
6701 Evenstad Drive
Maple Grove, MN 55369-6026

Sandoz, Inc.
Attn: Griha Lakshmi Mangru, M.S.
4700 Sandoz Drive
Wilson, NC 27893

Apotex Corp.
Attn: Kiran Krishnan
2400 North Commerce Parkway
Suite 400
Weston, FL 33326

2010 AUG 16 A 10:18

Re: Docket no. FDA-2007-N-0475[1]
PROPOSAL TO WITHDRAW MARKETING APPROVAL;
NOTICE OF OPPORTUNITY FOR A HEARING

Dear Midodrine HCl Application Holder:

The Food and Drug Administration (FDA or Agency) is proposing to withdraw approval of Shire Development, Inc.'s (Shire) ProAmatine (midodrine hydrochloride (HCl)) new drug application (NDA 19-815). Upon withdrawal of NDA 19-815, FDA will also withdraw approval of the following abbreviated new drug applications (ANDAs) for drug products containing midodrine HCl that reference NDA 19-815 as their reference listed drug: ANDA 77-746 held by Apotex Corp.; ANDA 76-449 held by Impax Laboratories, Inc.; ANDA 76-577 held by Mylan Pharmaceuticals, Inc.; ANDA 76-514 held by Sandoz, Inc.; and ANDA 76-725 held by Upsher-Smith Laboratories, Inc. This proposal is necessitated by Shire's failure to conduct postmarketing clinical trials (often referred to as phase 4 trials) that verify and describe the clinical benefit of midodrine HCl. If the Agency proceeds to withdraw approval of these products, any future use of midodrine HCl in the United States will require submission of an investigational new drug application to FDA. FDA will explore, as appropriate, continued availability of

[1] These issues were originally assigned docket number 2007N-0311. The number was changed to FDA-2007-N-0475 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

FDA-2007-N-0475

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midodrine HCl under our regulations governing expanded access, 21 CFR part 312, subpart I.[2]

I. Background

ProAmatine was approved for marketing under FDA's accelerated approval regulations, 21 CFR part 314, subpart H, on September 6, 1996, to treat patients with symptomatic orthostatic hypotension. Orthostatic hypotension is a condition in which patients are unable to maintain blood pressure in the upright position and thereby become dizzy or faint. Subpart H allows approval of drugs to treat serious or life-threatening illnesses based on a surrogate endpoint or a clinical endpoint other than survival or irreversible morbidity (§ 314.510). Approval of ProAmatine was based on trials that demonstrated that ProAmatine increased 1-minute standing systolic blood pressure, a surrogate marker considered likely to correspond to a clinical benefit, principally relief of symptoms of orthostatic hypotension and improved ability to perform life activities. At the time of approval, clinical benefit of ProAmatine was not established.

Section 314.510 specifies that such approval based upon surrogate endpoints is "subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit" in postmarketing studies. Shire's postmarketing study requirement was described in the company's NDA submissions and referenced in the Agency's approval letter dated September 6, 1996.

To date, no application or supplement containing the required postmarketing studies that verify the clinical benefit of midodrine HCl has been approved. At meetings and in correspondence with Shire and the ANDA holders, FDA has made clear that unless the required phase 4 trials were completed and successful and labeling describing clinical benefit approved, the Agency would withdraw approval of NDA 19-815 and all ANDAs referencing ProAmatine.

By letter dated August 12, 2009, to Shire and the holders of ANDAs for midodrine HCl products, FDA articulated the Agency's requirements regarding the postmarketing trials necessary to support efficacy of midodrine HCl. We stated that data should be derived from two randomized, double-blind, placebo-controlled trials, one to establish the effects of a single dose of midodrine HCl on the symptoms of orthostatic hypotension and a second trial to establish the presence of symptomatic benefit after at least 2 weeks of treatment. We directed Shire (and any ANDA holder intending to conduct phase 4 trials of midodrine HCl) to submit documentation of Institutional Review Board (IRB) approval and the proposed statistical analysis plans for both studies by February 12, 2010, and we required 50 percent enrollment in both trials by April 12, 2010, and 100 percent enrollment by June 12, 2010. Any application holder conducting phase 4 trials was expected to submit full study reports of the trials by October 12, 2010. We required that both trials be successful at a conventional ($p<0.05$) level of statistical significance for FDA to conclude that midodrine HCl effectively relieves symptoms of orthostatic hypotension. We advised you that if the specified deadlines were not met, FDA's Center

[2] 74 FR 40900, 40943 (August 13, 2009)

for Drug Evaluation and Research (CDER) would issue a notice of opportunity for a hearing on its proposal to withdraw approval of NDA 19-815 (and all ANDAs referencing NDA 19-815).

No application holder has satisfied the requirements set forth in our letter of August 12, 2009. Specifically, no application holder submitted documentation of IRB approval or statistical analysis plans for the two required studies on or before February 12, 2009, had 50 percent enrollment by April 12, 2010, or completed enrollment by June 12, 2010. To our knowledge, the required studies are not currently being conducted. In light of the foregoing and consistent with our authority under applicable provisions of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 301 et seq.) and implementing regulations, we now propose to withdraw approval of NDA 19-815. Upon withdrawal of NDA 19-815, FDA will also withdraw approval of all ANDAs that reference NDA 19-815.

II. Grounds for Withdrawal Under Both the Act and Implementing Regulations

Section 505(e) of the Act (21 U.S.C. 355(e)) provides statutory authority for FDA to withdraw approval of an NDA if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if an applicant has failed to maintain required records or make required reports. In addition, approval may be withdrawn if new information along with information considered when the application was approved shows the labeling to be false or misleading.

Section 505(j)(6) of the Act describes FDA's statutory authority to withdraw approval of an ANDA when the listed drug it references has been withdrawn under section 505(e). It provides "[i]f a drug [approved in an ANDA] refers in its approved application to a drug the approval of which was withdrawn or suspended [under section 505(e)] . . .the approval of the drug [approved in an ANDA] shall be withdrawn or suspended." Thus, under section 505(j)(6), if an ANDA refers to a listed drug that has been withdrawn under section 505(e) for failure to verify effectiveness, withdrawal of the ANDA under section 505(j)(6) will follow.

Section 506 of the Act (21 U.S.C. 356), added to the statute with the passage of the Food and Drug Administration Modernization Act of 1997 (FDAMA), describes the accelerated approval and expedited withdrawal procedures that apply to fast track products. It permits FDA to approve certain products based on a finding that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit. Under section 506(b)(2), such an approval may be subject to the requirement that "the sponsor conduct appropriate post-approval studies to validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint." Section 506(b)(3) also provides explicit authority for the Agency to use an expedited withdrawal procedure to withdraw approval of a product that has received an accelerated approval. Under this section, FDA can undertake an expedited withdrawal proceeding if, among other reasons, the application holder fails to conduct any required postapproval study with due diligence, or a postapproval study fails to verify clinical benefit. This provision

allows the Agency to withdraw approval using expedited procedures as described in FDA regulations.[3]

FDA's implementing regulations at 21 CFR 314.500 et seq. (also known as subpart H) describe the procedures for accelerated approval and expedited withdrawal of drugs for serious or life-threatening illnesses. They provide that FDA may grant marketing approval for a new drug product on the basis of "adequate and well-controlled clinical trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely . . . to predict clinical benefit." When a drug is approved using the accelerated approval mechanism described in subpart H of the regulations, approval is based on a weighing of the benefit suggested by and expected based on the effect of the drug on the surrogate endpoint against known and potential risks of the drug. As a condition of such approval, the application holder is required to submit additional postapproval clinical studies that verify clinical benefit.

If the effect on the surrogate endpoint does not translate into a clinical benefit or the clinical benefit cannot be verified, the risk/benefit assessment that supported initial approval of the drug changes significantly, and FDA may conclude that the drug no longer meets the safety and efficacy requirements for continued marketing under the Act. When this occurs, expedited withdrawal is generally in the public interest. Accordingly, the regulations provide that FDA may withdraw approval of a drug product approved under subpart H when "[a] postmarketing clinical study fails to verify clinical benefit[,]" if "[t]he applicant fails to perform the required postmarketing study with due diligence[,]" or "[o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use" (§ 314.530(a)(1), (a)(2), and (a)(6)). In the event that FDA withdraws an NDA for failure to verify effectiveness, the approval of an ANDA "identified in the notice of opportunity for hearing on the withdrawal of a listed drug will be withdrawn . . ." (21 CFR 314.151(b)(3)).[4]

Thus, a drug approved under the accelerated approval process may be withdrawn under these expedited withdrawal procedures if an application holder fails to conduct required postmarketing studies with due diligence or if the studies conducted fail to verify clinical benefit. The Agency's September 16, 1996, approval letter to Shire referred to the withdrawal provision of subpart H, stating "[i]f these studies do not provide verification of clinical benefit to conclude that the drug is safe and effective for an intended use, you will comply with the accelerated approval withdrawal procedures described in 21 CFR 314.530." Similarly, the Agency's approval letters to the ANDA applicants stated "if approval of the listed drug is withdrawn or suspended for any of the reasons specified in 21 CFR 314.530, the approval of your abbreviated new drug application (ANDA), which

[3] Although section 506 was not added to the Act until after approval of ProAmatine, its approach to accelerated approval and expedited withdrawal essentially codified FDA's preexisting regulations and is consistent with the approach taken here.

[4] The withdrawal provisions of section 506 of the Act and subpart H of the regulations do not explicitly address the status of ANDAs that rely on a reference listed drug approved based on a surrogate endpoint under § 314.510 when that reference listed drug is withdrawn under § 314.530. Section 505(j)(6) of the Act and § 314.151 of the regulations both address withdrawal of ANDAs when approval of the NDA for the reference listed drug is withdrawn.

relies on the finding of safety and effectiveness for the listed drug, may also be withdrawn pursuant to 21 CFR 314.150 and 314.151, or suspended prior to withdrawal pursuant to 21 CFR 314.153."

To date, neither Shire nor any of the midodrine HCl ANDA holders have submitted the data and information required to verify and describe the drug's clinical benefit, nor have they satisfied the specific requirements specified in the Agency's letter of August 12, 2009. Accordingly, we are hereby notifying Shire and all holders of midodrine HCl ANDAs, pursuant to sections 506 and 505(e) of the Act and under § 314.530(a) and (b) of the regulations, that CDER is proposing to withdraw the approval of NDA 19-815. Upon withdrawal of NDA 19-815, FDA will also withdraw approval of all ANDAs referencing NDA 19-815. We are hereby notifying Shire of an opportunity for hearing on the withdrawal of NDA 19-815, and we invite holders of ANDAs for midodrine HCl products to submit comments, as described in section III.B of this letter.

III. Notice of Opportunity for a Hearing and Submission of Written Comments

A. Submissions by NDA Holder

In accordance with 21 CFR 314.530(b), the Director of CDER hereby provides Shire with notice of an opportunity for a hearing on CDER's proposal to withdraw approval of NDA 19-815, the grounds for which are described in section II of this letter. Shire may file a written request for a hearing within 15 days of receipt of this letter. If Shire fails to file a written request for a hearing within 15 days, Shire will thereby waive its opportunity for a hearing. The failure of an applicant to file a timely request for a hearing constitutes an election by that applicant not to avail itself of the opportunity to request a hearing concerning the action proposed and constitutes a waiver of any contentions concerning the legal status of that applicant's drug product. In such instance, FDA intends to withdraw approval of the affected application(s) and to take other appropriate action. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

If Shire files a timely request for a hearing, the company must, within 30 days of receipt of this letter, submit data, information, and analyses to demonstrate that there is a genuine and substantial issue of material fact that requires a hearing. A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of material fact that requires a hearing. If it conclusively appears on the face of the data, information, and analyses submitted that there is no genuine and substantial issue of material fact, or if the required data, information, and analyses are not provided, the hearing request will not be granted. If a hearing is granted, it will be conducted according to the procedures outlined in part 15 of FDA regulations (21 CFR part 15), as modified by § 314.530(e), and the Commissioner's decision will constitute final Agency action subject to judicial review (§ 314.530(f)).

Paper submissions under this notice of opportunity for a hearing must be filed in four copies. Please submit written requests for a hearing; any data, information, and analyses

justifying a hearing; and any other comments identified with Docket No. FDA-2007-N-0475 to:

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Please submit electronic requests for a hearing; any data, information, and analyses justifying a hearing; and any other comments identified with Docket No. FDA-2007-N-0475 to *http://www.regulations.gov*.

Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and on the Internet at *http://www.regulations.gov*.

B. Submissions by ANDA Holders

This letter serves as notice to the identified ANDA holders that the Agency proposes to withdraw approval of their applications upon withdrawal of approval of the listed drug. Consistent with § 314.151 (as modified by the accelerated withdrawal provisions in § 314.530), the identified ANDA holders may submit written comments on this notice of opportunity for hearing. ANDA holders are required to submit comments within 30 days of receipt of this letter so that they may be considered by the Agency, along with any request and justification submitted by the NDA holder, in making a decision whether to hold a hearing. If a hearing is granted, those ANDA holders who submitted timely comments may participate in the hearing as nonparty participants.

If an ANDA holder has submitted timely comments but does not have an opportunity to participate in a hearing because a hearing is not held, the submitted comments will be considered by the Agency (§ 314.151(c)(1)). After considering all timely submissions, the Agency will issue an initial decision. The initial decision will respond to comments and contain the Agency's preliminary decision whether there are grounds to withdraw approval of the listed drug and the ANDAs. The initial decision will be sent to each ANDA holder that submitted comments (§ 314.151(c)(1)). ANDA holders to whom the initial decision is sent may, within 30 days of the issuance of the initial decision, submit written objections (§ 314.151(c)(2)). The Agency may, at its discretion, hold a limited oral hearing to resolve dispositive factual issues that cannot be resolved on the basis of written submissions (§ 314.151(c)(3)). If there are no timely objections, the initial decision will become final at the expiration of 30 days (§ 314.151(c)(4)). If timely objections are submitted, they will be reviewed and addressed in a final decision (§ 314.151(c)(5)).

If, upon withdrawal of approval of the listed drug, the Agency determines that the grounds for withdrawal of the listed drug are not applicable to one or more identified

ANDAs, approval of those ANDAs will not be withdrawn (§ 314.151(d)). In all other cases, approval of the identified ANDAs will be withdrawn upon the issuance of a final decision concluding that the listed drug should be withdrawn. The final decision will be in writing and will constitute final Agency action, reviewable in a judicial proceeding (§ 314.151(c)(7)).

Paper submissions of written comments must be filed in four copies. Please submit written comments identified with Docket No. FDA-2007-N-0475 to:

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

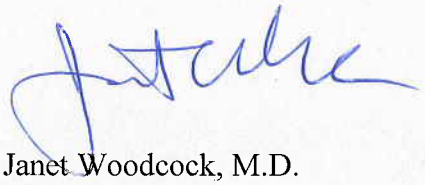
Please submit comments in electronic form identified with Docket No. FDA-2007-N-0475 to *http://www.regulations.gov*.

Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and on the Internet at *http://www.regulations.gov*.

IV. Authority and Contact Information

This notice is issued under § 314.530(b) and under authority delegated to the Director of CDER at FDA. If you have questions regarding this notice, please contact Quynh Nguyen, Pharm.D., RAC, at (301) 796-2240.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19815	ORIG-1	SHIRE DEVELOPMENT INC	PROAMATINE
ANDA-77746	ORIG-1	APOTEX INC ETOBICOKE SITE	MIDODRINE HYDROCHLORIDE
ANDA-76449	ORIG-1	IMPAX PHARMACEUTICALS	MIDODRINE HYDROCHLORIDE
ANDA-76577	ORIG-1	MYLAN PHARMACEUTICALS INC	MIDODRINE HYDROCHLORIDE
ANDA-76514	ORIG-1	SANDOZ INC	MIDODRINE HYDROCHLORIDE
ANDA-76725	ORIG-1	UPSHER SMITH LABORATORIES INC	MIDODRINE HYDROCHLORIDE

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/s/

QUYNH M NGUYEN
08/16/2010
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